



## Letter to the Editor

## Pregnancy outcomes and cytomegalovirus DNAemia in HIV-infected pregnant women with CMV

Sir,

It is well known that cytomegalovirus (CMV) coinfection affects a large proportion of people with HIV, with a significant impact on disease progression and survival [1]. In HIV-CMV coinfecting pregnant women, however, few studies have been conducted: maternal immunosuppression has been linked to a higher risk of CMV infant infection, and CMV DNAemia to higher maternal and infant mortality [2,3]. Overall, little is known about pregnancy outcomes and CMV viraemia in CMV-coinfecting pregnant women with HIV. To further explore this issue, the impact of CMV coinfection was evaluated on pregnancy outcomes in a national cohort of pregnant women with HIV, assessing in a study subsample the prevalence and correlates of CMV DNAemia in HIV-CMV coinfecting pregnant women.

Data from the Italian National Program on Surveillance on Anti-retroviral Treatment in Pregnancy were used [4], considering all HIV-infected women with known CMV serostatus. The main pregnancy outcomes were compared between women with and without positive serology for CMV, and plasma CMV-DNA levels were evaluated in a subset of CMV-positive women who had given specific consent to virological evaluations and had evaluable plasma samples. The cases were analysed retrospectively, and no systematic screening for CMV infection was conducted in infants. Ethics approval was obtained from the ethics committee of the I.N.M.I. Lazzaro Spallanzani in Rome; ref. deliberations: 578/2001 (28 September 2001) and 7/2003 (26 February 2003). Plasma CMV-DNA was quantified with the kPCR PLX Cytomegalovirus DNA assay (Siemens Healthcare) using the VERSANT kPCR Molecular System (Siemens), with a detection limit of 214.6 (2.33 log) IU/mL. Quantitative data were compared by the Mann-Whitney *U* test and proportions by the chi-square test, with OR and 95% CI calculated. A *p*-value below 0.05 was considered to be significant, using for all analyses the SPSS software, version 22.0 (IBM Corp, Released 2013, Armonk, NY, USA).

As of 21 March 2016, among 2250 pregnancies with available information on CMV serostatus (62% of all cases in the database, including ongoing pregnancies and cases lost to follow-up), 1490 were CMV antibody-positive (66.2%). Women with and without positive serology for CMV were similar for age, CD4 counts, CDC-HIV disease stage, parity, antiretroviral treatment experience, and treatment status at conception. No differences between the two groups were found for the main pregnancy outcomes, represented by miscarriage or fetal demise, preterm delivery, low (<2500g) or very low (<1500g) birthweight, intrauterine growth restriction (gender- and gestational age-adjusted Z-score for birthweight <10<sup>th</sup> percentile), major birth defects, delivery complications, and

HIV transmission (Table 1). Among 1126 infants from CMV-positive mothers with available information on clinical status, three neonatal cases of CMV infection were reported.

Among the 1490 women positive for CMV antibodies, 123 (8.3%) had available plasma samples collected during pregnancy, usually (90.2%) after the first trimester, which were evaluated for CMV-DNA quantitation. None of these women had clinical signs of new viral infection or viral reactivation during pregnancy. Only four of them (3.3%) had positive CMV DNAemia in plasma, all at very low levels (range 2.35–2.61 log IU/mL). None of these four women had low (<200/mm<sup>3</sup>) CD4 counts (range 270–852), and all had normal pregnancy outcomes, with no preterm delivery, low birthweight, birth defects, CMV or HIV transmission reported. Interestingly, all the four mothers had detectable HIV in plasma at third trimester (range 99–20 004 copies/mL).

This study showed that in a large cohort of pregnant women with HIV, roughly two-thirds had positive serology for CMV, with no adverse consequences of coinfection on the main pregnancy outcomes. This rate is almost identical to that observed in two different studies conducted among a general population of pregnant women in Northern and Southern Italy, who showed prevalences of positive CMV serology of 68.3% (1925/2817) and 65.9% (595/797), respectively [5,6], suggesting similar CMV prevalence for HIV-negative and HIV-positive pregnant women. It was also shown in a nested evaluation that among pregnant women with HIV with positive serology for CMV and no signs of primary infection, a small proportion (4/123, 3.3%) have detectable CMV DNAemia, usually at low levels. This figure is consistent with published data in an HIV-CMV coinfecting African population, in whom rate of detectable CMV in plasma was 4.8% (7/146) [7], suggesting slightly higher rate of CMV DNAemia among pregnant women with HIV compared with the general population. In a previous Italian study on a general population of CMV IgG-positive pregnant women with no evidence of primary infection, 0.5% (4/774) had positive, low-level CMV DNAemia [8]. A similar rate (2/134, 1.4%) was found in an unselected population of Turkish pregnant women [9]. Detectable low-level CMV DNAemia could represent either subclinical viral reactivation or the terminal phase of blood viral clearance after a recent primary infection. It is unknown whether partial immunosuppression in pregnant women with HIV may be responsible for low-level CMV replication and detectable DNAemia, and it was not possible to define timing of CMV infection by antibody avidity testing or evaluation of CMV-specific IgM. In any case, asymptomatic maternal CMV DNAemia in a context of relatively preserved CD4 counts seems to represent for pregnant women

**Table 1**  
Characteristics and pregnancy outcomes according to CMV serostatus

Women's characteristics	CMV-positive		CMV-negative		p-value <sup>a</sup>
	N		N		
Age, years (n: 2245)	1486		759		0.924
CD4 cell count, cells/mm <sup>3</sup> (n: 1453) <sup>b</sup>	998		455		0.978
	n/N	%	n/N	%	
At least one previous pregnancy (n: 2218)	1090/1467	74.3	551/751	73.4	0.636
History of AIDS-defining events (n: 2220)	84/1470	5.7	45/750	6.0	0.785
Antiretroviral-treatment experienced (n: 2185)	929/1447	64.2	504/738	68.3	0.057
On treatment at conception (n: 2225)	777/1475	52.7	390/750	52.0	0.762
Pregnancy outcomes					
Miscarriage or fetal demise (n: 1941)	95/1313	7.2	56/628	8.9	0.797
Preterm delivery (n: 1672)	234/1152	20.3	108/520	20.8	0.972
Low birthweight (<2500 g) (n: 1576, twins included)	250/1082	23.1	101/494	20.4	1.169
Very low birthweight (<1500 g) (n: 1576, twins included)	37/1082	3.4	11/494	2.2	1.555
Small by gestational age (<10 <sup>th</sup> percentile) (n: 1516, singletons only)	130/1034	12.6	53/482	11.0	1.164
Complications of delivery <sup>d</sup> (n: 1606)	85/1100	7.7	37/506	7.3	1.062
Major birth defects (n: 1616)	39/1108	3.5	17/508	3.3	1.054
HIV transmission (n: 1235)	14/857	1.6	8/370	2.1	0.768

IQR, interquartile range; ARV, antiretroviral therapy.

<sup>a</sup> Mann-Whitney U test for quantitative variables and chi-square test for categorical variables.

<sup>b</sup> Second trimester.

<sup>c</sup> Reference category: CMV-positive.

<sup>d</sup> Usually represented by surgical wound infections and fever.

with HIV an infrequent condition not associated with major clinical consequences.

### The Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy

*Project coordinators:* M. Floridia, M. Ravizza, E. Tamburrini.

*Participants:* M. Ravizza, E. Tamburrini, F. Mori, P. Ortolani, E.R. dalle Nogare, F. Di Lorenzo, G. Sterrantino, M. Meli, S. Polemi, J. Nocentini, M. Baldini, G. Montorzi, M. Mazzetti, P. Rogasi, B. Borch, F. Vichi, B. Del Pin, E. Pinter, E. Anzalone, R. Marocco, C. Mastroianni, V.S. Mercurio, A. Carocci, E. Grilli, A. Maccabruni, M. Zaramella, B. Mariani, G. Natalini Raponi, G. Guaraldi, G. Nardini, C. Stentarelli, B. Beghetto, A.M. Degli Antoni, A. Molinari, M.P. Crisalli, A. Donisi, M. Piepoli, V. Cerri, G. Zuccotti, V. Giacommet, S. Coletto, F. Di Nello, C. Madia, G. Placido, A. Vivarelli, P. Castelli, F. Savalli, V. Portelli, F. Sabbatini, D. Francisci, L. Bernini, P. Grossi, L. Rizzi, S. Alberico, G. Maso, M. Airoud, G. Soppelsa, A. Meloni, M. Dedoni, C. Cuboni, F. Ortu, P. Piano, A. Citernes, I. Bordoni Vicini, K. Luzi, A. Spinillo, M. Roccio, A. Vimercati, A. Miccolis, A. De Gennaro, B. Guerra, F. Cervi, G. Simonazzi, E. Margarito, M.G. Capretti, C. Marsico, G. Faldella, M. Sansone, P. Martinelli, A. Agangi, A. Capone, G.M. Maruotti, C. Tibaldi, L. Trentini, T. Todros, G. Masuelli, V. Frisina, I. Cetin, T. Brambilla, V. Savasi, C. Personeni, C. Giaquinto, M. Fiscon, E. Rubino, A. Bucceri, R. Matrone, G. Scaravelli, O. Genovese, C. Cafforio, C. Pinnetti, G. Liuzzi, V. Tozzi, P. Massetti, A.M. Casadei, A.F. Cavaliere, M. Cellini, G. Castelli Gattinara, A.M. Marconi, S. Dalzero, V. Sacchi, M. Ierardi, C. Polizzi, A. Mattei, M.F. Pirillo, R. Amici, C.M. Galluzzo, S. Donnini, S. Baroncelli, M. Floridia.

*Pharmacokinetics:* P. Villani, M. Cusato.

*Advisory Board:* A. Cerioli, M. De Martino, P. Mastroiacovo, F. Parazzini, E. Tamburrini, S. Vella.

*SIGO-HIV Group National Coordinators:* P. Martinelli, M. Ravizza.

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### References

- [1] Deayton JR, Sabin CA, Johnson MA, Emery VC, Wilson P, Griffiths PD. Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy. *Lancet* 2004;363:2116–21.
- [2] Slyker JA, Lohman-Payne BL, Rowland-Jones SL, Otieno P, Maleche-Obimbo E, Richardson B, et al. The detection of cytomegalovirus DNA in maternal plasma is associated with mortality in HIV-1-infected women and their infants. *AIDS* 2009;23:117–24.
- [3] Forner G, Abate D, Mengoli C, Palù G, Gussetti N. High Cytomegalovirus (CMV) DNAemia Predicts CMV Sequelae in Asymptomatic Congenitally Infected Newborns Born to Women With Primary Infection During Pregnancy. *J Infect Dis* 2015;212:67–71.
- [4] Floridia M, Ravizza M, Tamburrini E, Anzidei G, Tibaldi C, Maccabruni A, et al. Diagnosis of HIV infection in pregnancy: data from a national cohort of pregnant women with HIV in Italy. *Epidemiol Infect* 2006;134:1120–7.
- [5] De Paschale M, Agrappi C, Manco MT, Paganini A, Clerici P. Incidence and risk of cytomegalovirus infection during pregnancy in an urban area of Northern Italy. *Infect Dis Obstet Gynecol* 2009;2009:206505.
- [6] Puccio G, Cajozzo C, Canduscio LA, Cino L, Romano A, Schimmenti MG, et al. Epidemiology of Toxoplasma and CMV serology and of GBS colonization in pregnancy and neonatal outcome in a Sicilian population. *Ital J Pediatr* 2014;40:23.
- [7] Slyker J, Farquhar C, Atkinson C, Ásbjörnsdóttir K, Roxby A, Drake A, et al. Compartmentalized cytomegalovirus replication and transmission in the setting of maternal HIV-1 infection. *Clin Infect Dis* 2014;58:564–72.
- [8] Revello MG, Furione M, Rognoni V, Arossa A, Gerna G. Cytomegalovirus DNAemia in pregnant women. *J Clin Virol* 2014;61:590–2.
- [9] Dinc B, Bozdayi G, Biri A, Kalkanci A, Dogan B, Bozkurt N, et al. Molecular detection of cytomegalovirus, herpes simplex virus 2, human papillomavirus 16–18 in Turkish pregnant. *Braz J Infect Dis* 2010;14:569–74.

M. Floridia\*, M.F. Pirillo  
Department of Therapeutic Research and Medicines Evaluation,  
Istituto Superiore di Sanità, Rome, Italy

A. Degli Antoni, A. Molinari  
*Department of Infectious Diseases and Hepatology, Azienda  
Ospedaliera di Parma, Italy*

E. Tamburrini  
*Department of Infectious Diseases, Catholic University,  
Rome, Italy*

C. Pinnetti  
*I.N.M.I. Lazzaro Spallanzani, Rome, Italy*

G. Guaraldi, G. Nardini  
*Department of Medical Specialties, Infectious Diseases Clinic,  
University of Modena and Reggio Emilia, Modena, Italy*

G. Masuelli  
*Department of Obstetrics and Neonatology, Città della Salute e della  
Scienza Hospital, and University of Turin, Italy*

S. Dalzero  
*Department of Obstetrics and Gynaecology, DMSD San Paolo Hospital  
Medical School, University of Milan, Italy*

I. Cetin  
*Department of Obstetrics and Gynaecology, Luigi Sacco Hospital and  
University of Milan, Italy*

M. Sansone  
*Department of Neurosciences, Reproductive and Dentistry Science,  
University Federico II, Naples, Italy*

R. Amici  
*Department of Therapeutic Research and Medicines Evaluation,  
Istituto Superiore di Sanità, Rome, Italy*

M. Ravizza, on behalf of The Italian Group on Surveillance on  
Antiretroviral Treatment in Pregnancy  
*Department of Obstetrics and Gynaecology, DMSD San Paolo Hospital  
Medical School, University of Milan, Italy*

\* Corresponding author. Marco Floridia, Department of Therapeutic  
Research and Medicines Evaluation, Istituto Superiore di Sanità,  
Viale Regina Elena 299, 00161 Rome, Italy.  
E-mail address: [marco.floridia@iss.it](mailto:marco.floridia@iss.it) (M. Floridia).

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